



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.         | CONFIRMATION NO.       |
|--|-------------|----------------------|-----------------------------|------------------------|
| 10/528,304   | 03/17/2005  | Stephen D. Goble     | 21030P                      | 6448                   |
| 210 7590 01/29/2008<br>MERCK AND CO., INC<br>P O BOX 2000<br>RAHWAY, NJ 07065-0907 |             |                      | EXAMINER<br>O'DELL, DAVID K |                        |
|  |             |                      | ART UNIT<br>1625            | PAPER NUMBER           |
|  |             |                      | MAIL DATE<br>01/29/2008     | DELIVERY MODE<br>PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



### DETAILED ACTION

1. This application is a 371 of This application is a 371 of PCT/US03/34002 filed 10/24/2003 which claims priority to U.S. Provisional 60/422,447 filed 10/30/2002.

Claims 1-22 are pending.

### *Response to Restriction Election*

2. Applicant's election of group I and the species (the compound of Example 1) in the reply filed on December 26, 2007 is acknowledged. The election was made with traverse, and the examiner finds the arguments persuasive with respect to R<sup>1</sup>. Applicant's representative has argued that the examiner should not have restricted on the R<sup>1</sup> variable. Based on applicant's argument's and general statement that alkyl is obvious over another substituted alkyl (i.e. CF<sub>3</sub> is the same as alkyl), the restriction requirement on R<sup>1</sup> is withdrawn. This admission on the record may form the basis of an obviousness rejection, where any prior art substituted alkyl is found. This application contains claims drawn to a nonelected invention. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

#### New Restriction Requirement:

Group I, Claims 1-18 drawn to compounds and compositions where in claim 1 Formula I, n is 1, R<sub>2</sub> is benzyl. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group II, Claims 1-18 drawn to compounds and compositions not in Group I. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group III, Claims 19-22 drawn to methods of treatment limited in scope to a single group I-II. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 17 :

15                    17.    A compound which is selected from the group consisting of the title  
compounds of the Examples, and pharmaceutically acceptable salts and individual diastereomers  
thereof.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.        Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement

Art Unit: 1625

requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

- (A) The breadth of the claims;*
- (B) The nature of the invention;*
- (C) The state of the prior art;*
- (D) The level of one of ordinary skill;*
- (E) The level of predictability in the art;*
- (F) The amount of direction provided by the inventor;*
- (G) The existence of working examples; and*
- (H) The quantity of experimentation needed to make or use the invention*

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

**(A) The breadth of the claims:** The claims are very broad encompassing all heterocycles, carbocycles and other groups bearing multiple substitutions of unascertainable structure. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at CCR2 receptor. **(D) The level of one of ordinary skill:** One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art:** **(E) The level of predictability in the art:** **(F) The amount of direction provided by the inventor,** **(G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (C, E-H) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structure I.

While chemical limitations are important more significant are the limitations of activity at CCR2. What are the important structural features for the claimed utility? It is clear from the data in the specification that the structural features of the compound are of paramount importance for activity. Could the applicant please clarify on the record whether or not the

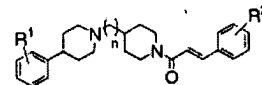
Art Unit: 1625

structure is important for the claimed utility. The only information in the specification as to what the molecular determinants are for activity at CCR2 receptor is reproduced here:

30 In particular, the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an  $IC_{50}$  of less than about 1  $\mu M$ . Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

What does “generally with an  $IC_{50}$  of less than about 1  $\mu M$ ” mean? In what cases does this generalization not hold true? While the paucity of compounds in the specification (only 64), and no data make a complete evaluation impossible, all the compounds have at least one trifluoromethyl group on the benzyl group and no substituents other than H, F or OH. (H) The medicinal chemistry of CCR2 is relatively well-developed and many limitations are well known in the art. It is sensitive to structural changes that may be relatively minor in the chemical sense see Xia et. al. “Synthesis and biological evaluation of phenyl piperidine derivatives as CCR2 antagonists” *Bioorganic & Medicinal Chemistry Letters* **2007**, 17, 5964-5968, whole document. In particular compound **3m** is essentially inactive at 25  $\mu M$  and differs from potent antagonists only by the identity and position of a halogen atom.

Table 2. Analogs containing a second piperidine ring of structure 3 from Figure 1



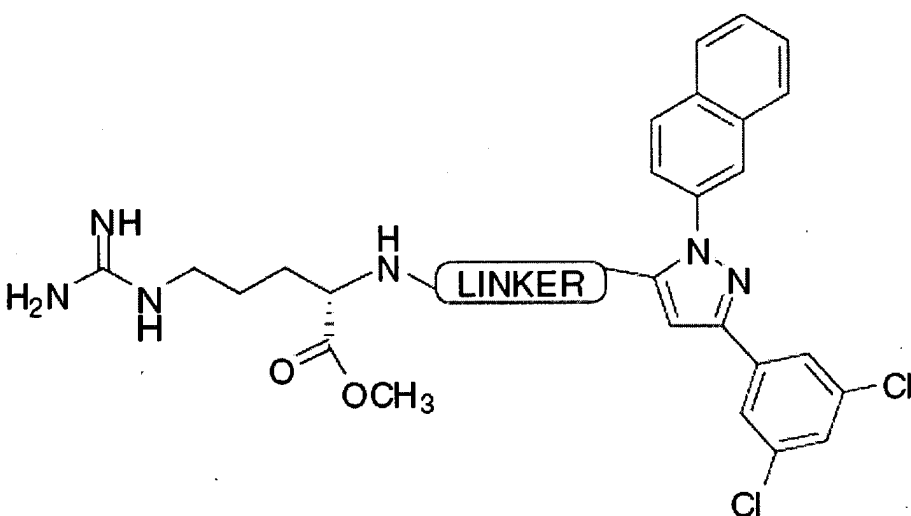
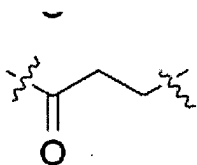
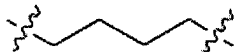
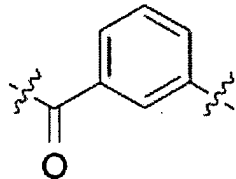
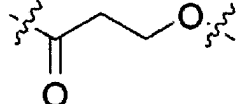
| Compound | R <sup>1</sup>  | n | R <sup>2</sup>    | CCR2B binding $IC_{50}$ ( $\mu M$ ) |
|----------|-----------------|---|-------------------|-------------------------------------|
| 3a       | 2-Methoxy       | 1 | 3,4-Dichloro      | 11.1                                |
| 3b       | 3-Methoxy       | 1 | 3,4-Dichloro      | 4.0                                 |
| 3c       | 4-Methoxy       | 1 | 3,4-Dichloro      | 0.32                                |
| 3d       | 4-Dimethylamino | 1 | 3,4-Dichloro      | 0.95                                |
| 3e       | 4-Hydroxy       | 1 | 3,4-Dichloro      | 0.51                                |
| 3f       | 4-Methyl        | 1 | 3,4-Dichloro      | 2.2                                 |
| 3g       | 4-Chloro        | 1 | 3,4-Dichloro      | 0.30                                |
| 3h       | 4-Chloro        | 1 | 3,4-Difluoro      | 2.0                                 |
| 3j       | 4-Chloro        | 1 | 3,4-Dimethoxy     | 5.9                                 |
| 3k       | 4-Chloro        | 1 | 3-Trifluoromethyl | 1.4                                 |
| 3l       | 4-Chloro        | 1 | 4-Bromo           | 5.2                                 |
| 3m       | 4-Chloro        | 1 | 2-Fluoro-4-bromo  | 17% at 25 $\mu M$                   |
| 3n       | 4-Chloro        | 2 | 3,4-Dichloro      | 2.9                                 |

Art Unit: 1625

In Anthony B. Pinkerton "Diaryl substituted pyrazoles as potent CCR2 receptor antagonists" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 807–813, a study of structure activity relationships reveals the unpredictable and sensitive nature of CCR2 ligands to the structure of the compound:

Art Unit: 1625

**Table 2.** Linker modifications

|  |   |  |                                     |
|--|---|--|-------------------------------------|
| Compound   | LINKER  | CCR2 IC <sub>50</sub><br>(nM) <sup>a</sup> | Chemotaxis IC <sub>50</sub><br>(nM) |
| 30   |  | 4741                                       | NT <sup>c</sup>                     |
| 31   |  | NA <sup>b</sup>                            | NT <sup>c</sup>                     |
| 32   |  | NA <sup>b</sup>                            | NT <sup>c</sup>                     |
| 33   |  | 62   | 118                                 |

<sup>b</sup> NA denotes not active <10  $\mu$ M concentration.



Replacement of an ethyl group in **30** for a phenyl in **32** gave inactive compounds.

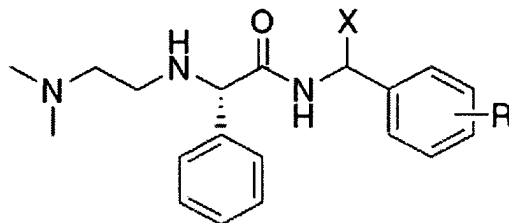
Where the author stated, “It appears that the SAR is relatively tight for modifications in this area. For example, shortening the chain one carbon, as in **30**, leads to a precipitous drop in activity to 4741 nM. Analog **31** highlights the importance of the central amide for potency—removal of the carbonyl gives a compound that is inactive. Likewise, constraining the linker as in phenyl analog **32** gives an inactive compound.”

Perhaps more tellingly are compounds developed by Yang et. al. which are remarkably similar to those of the instant case, Yang et. al. “Discovery of 3,5-bis(trifluoromethyl)benzyl L-arylglycinamide based potent CCR2 antagonists” *Bioorganic & Medicinal Chemistry Letters* **2006**, *16*, 3735–3739. An SAR of the benzylic amide moiety, revealed severe restraints upon the identity of the substituents,

**“The bis-trifluoromethylbenzyl group is extremely sensitive to modification (Table 2). Both of the CF<sub>3</sub> groups are critical for activity. Attempts to replace the bis-trifluoromethylbenzyl group with other substituted benzyl groups resulted in inactive compounds (24–27) as shown in Table 2. The introduction of a methyl at the benzylic position is a way of restricting the number of low-energy conformations at this region, potentially favoring a more active conformation. Unfortunately, in this instance it greatly reduced the binding of compound 28 as compared with the parent 13.”**

Table 2 is reproduced below for convenience:

**Table 2.** Binding affinity to human CCR2 (CHO).



| Compound | X  | R                     | Binding IC <sub>50</sub> (nM) |
|----------|----|-----------------------|-------------------------------|
| 24       | H  | 2-CF <sub>3</sub>     | 1%                            |
| 25       | H  | 3-CF <sub>3</sub>     | 5%                            |
| 26       | H  | 4-CF <sub>3</sub>     | 7%                            |
| 27       | H  | 3,5-DiMe              | 0%                            |
| 28       | Me | 3,5-DiCF <sub>3</sub> | 28%                           |
| 13       | H  | 3,5-DiCF <sub>3</sub> | 1000                          |

% inhibition at 1  $\mu$ M when no IC<sub>50</sub>'s were measured.

We have been given no information in regard to the molecular determinants of receptor affinity for the compounds of the instant case, however at least for the CF<sub>3</sub> benzyl group the identity cannot be changed and maintain activity. (F & G) In this case these compounds bear a structural resemblance to one another, yet the claims are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only

Art Unit: 1625

64 examples (that may or may not have activity at CCR2) in this unpredictable art without undue experimentation. (C, E, F, G, H).

***Conclusion***

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

**RITA DESAI  
PRIMARY EXAMINER**

*RDesai*  
1/24/08

Application/Control Number: 10/528,304

Page 11

Art Unit: 1625